General

Guideline Title

Endometrial cancer.

Bibliographic Source(s)

Alberta Provincial Gynecologic Oncology Tumour Team. Endometrial cancer. Edmonton (Alberta): CancerControl Alberta; 2013 Sep. 15 p. (Clinical practice guideline; no. GYNE-002). [76 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Gynecologic Oncology Tumour Team. Endometrial cancer. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2012 Apr. 16 p. (Clinical practice guideline; no. GYNE-002).

Recommendations

Major Recommendations

The following recommendations were considered when developing the recommendations: National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), the British Columbia Cancer Agency (BCCA), and Cancer Care Ontario (CCO) as per Fédération Internationale de Gynecologie et d'Obstétrique (FIGO) Staging (2010). A detailed description of this staging system can be found in the Appendix of the original guideline document.

Surgery

A pathology review should be performed by a pathologist with experience in gynecologic pathology.

As the majority of patients is diagnosed with adenocarcinomas and is diagnosed in early stage, the standard treatment is a hysterectomy with bilateral salpingo-oophorectomy (BSO) with or without lymph node dissection. Patients should be referred to the gynecologic oncologists at the Cross Cancer Institute, Edmonton or the Tom Baker Cancer Centre, Calgary if the adenocarcinoma is grade II or greater and if it is a clinical stage II or greater.

Papillary serous, clear cell carcinomas, and carcinosarcomas of the uterus require a comprehensive staging procedure which includes a hysterectomy, BSO, pelvic and para-aortic lymph node dissection, and an omentectomy (Gien et al., 2007). These patients also need referral to the gynecologic oncologists.

For clinically obvious cervix involvement, referral to the cancer centre is warranted for consideration of a radical hysterectomy, BSO with

lymphadenectomy, OR preoperative radiotherapy followed by a simple hysterectomy with BSO. For *medically unfit patients*, where surgery is not an option, treatment may include radiotherapy alone or with hormonal therapy and/or chemotherapy.

Adjuvant Treatment for Completely Surgically Staged Adenocarcinoma (as per FIGO, 2010)

Stage IA

The majority (70%) of patients will present with a grade 1 or 2 tumour, while about 30% will present with a grade 3 tumour. Treatment can vary, depending on the presence of adverse risk factors. These include positive lymphovascular invasion, tumour size, and cervical glandular involvement and age >65 years.

- Grade 1: observe/no adjuvant treatment
- Grade 2: observe/no adjuvant treatment or vaginal vault brachytherapy can be considered if patient has lymphovascular space involvement (LVSI) or based on patient age
- Grade 3: vaginal brachytherapy if adverse risk factors are present (30% of stage 1A grade 3 patients)
- OR if patient has LVSI, consider enrolment in PORTEC-3/EN.7 Trial

Stage IB

Approximately 35% of all patients with endometrial cancer will present with a stage IB.

- Grade 1: vaginal vault brachytherapy can be offered
- Grade 2: vaginal vault brachytherapy
- Grade 3: whole pelvic radiation therapy or vaginal vault brachytherapy (consideration of chemotherapy to be discussed in a multidisciplinary setting)
- OR consider enrolment in PORTEC-3/EN.7 Trial

Stage II

Approximately 10% of all patients with endometrial cancer will present with a stage II tumour. For clinically obvious cervix involvement, consider a radical hysterectomy, BSO with lymphadenectomy, OR preoperative radiotherapy followed by a simple hysterectomy with BSO. In the case of stage II disease where pre-operative radiotherapy is given, intracavitary radiotherapy is usually given in addition to external beam radiotherapy (EBRT).

Postoperative management:

- Grade 1: Options include:
  - Observe/no treatment if radical hysterectomy, BSO, and pelvic lymphadenectomy done; otherwise, treat with pelvic radiotherapy plus vaginal brachytherapy
  - OR consider enrolment in PORTEC-3/EN.7 Trial (macroscopic stage II for which radical hysterectomy has been carried out are excluded)
- Grade 2: Options include:
  - Treat with pelvic radiotherapy plus vaginal brachytherapy
  - OR consider enrolment in PORTEC-3/EN.7 Trial (macroscopic stage II for which radical hysterectomy has been carried out are excluded)
- Grade 3: Options include:
  - Treat with pelvic radiotherapy plus vaginal brachytherapy
  - OR consider enrolment in PORTEC-3/EN.7 Trial (macroscopic stage II for which radical hysterectomy has been carried out are excluded)

Stage III

Approximately 20% of all patients with endometrial cancer will present with a stage III tumour.

Stages IIIA and IIIB

- Grades 1/2/3: Options include:
  - Chemotherapy +/- radiotherapy +/- hormone therapy
  - OR Adjuvant radiotherapy +/- chemotherapy +/- hormone therapy
  - OR Pelvic radiotherapy +/- vaginal brachytherapy

- OR enrolment in PORTEC-3/EN.7 Trial

Stages IIIC1 and IIIC2

- Grades 1/2/3: Options include:
  - Chemotherapy +/- EBRT +/- vaginal brachytherapy +/- hormone therapy
  - OR enrolment in PORTEC-3/EN.7 Trial

Stage IV

Approximately 10% of all patients with endometrial cancer will present with a stage IV tumour.

Stage IVA

- Options include:
  - Chemotherapy +/- hormone therapy +/- pelvic EBRT
  - Participation in clinical trials is strongly encouraged

Stage IVB

- Options include:
  - Chemotherapy +/- hormone therapy +/- consideration of palliative radiotherapy
  - Participation in clinical trials is strongly encouraged

Positive cytology (for completely staged patients with no other extrauterine disease)

- Grades 1/2/3: Options include:
  - Observe or consider vaginal brachytherapy or pelvic radiotherapy (RT) +/- vaginal brachytherapy +/- chemotherapy if there are other prognostic factors
  - OR enrolment in PORTEC-3/EN.7 Trial

Recommended Chemotherapy

Four to six cycles of carboplatin (area under the curve [AUC] 5) with paclitaxel at 175 mg/m^2. In the case of hypersensitivity to paclitaxel, docetaxel at 75 mg/m^2 should be considered.

Recommended Hormone Therapy

The recommended medications are medroxyprogesterone (Provera) 200–400 mg daily or Megestrol (Megace) 160 mg daily.

<u>Adjuvant Treatment for Surgically Staged Papillary Serous and Clear Cell Carcinomas</u>

Stage IA

- Options include:
  - Observe if there is no myometrial invasion +/- vaginal brachytherapy for grade 3
  - OR chemotherapy +/- vaginal brachytherapy if there is myometrial invasion
  - OR enrolment in PORTEC-3/EN.7 Trial

Stage IB, Stage II

- Options include:
  - Chemotherapy +/- RT
  - OR enrolment in PORTEC-3/EN.7 Trial

Stage III, Stage IV (Adequately Debulked)

- Options include:
  - Chemotherapy +/- RT
  - OR enrolment in PORTEC-3/EN.7 Trial (only eligible if microscopic residual disease)

Recommended Chemotherapy

Four to six cycles of carboplatin (AUC 5) with paclitaxel at 175 mg/m^2. In the case of hypersensitivity to paclitaxel, docetaxel at 75 mg/m^2 should be considered.

Adjuvant Treatment for Incompletely Surgically Staged Patients

A computed tomography (CT) scan of the chest, abdomen and pelvis is recommended.

Consider reoperating for surgical staging.

Stage IB

- Grades 1/2: Options include:
  - If radiologic imaging is negative, treat with vaginal brachytherapy +/- pelvic radiotherapy
  - If radiologic imaging is positive, surgically restage and then treat as for completely surgically staged patients (as above)
- Grade 3: Options include:
  - If radiologic imaging is negative, treat with pelvic radiotherapy and vaginal brachytherapy +/- para-aortic radiotherapy. For grade 3 tumours, chemotherapy may be added
  - If radiologic imaging is positive, consider surgical restaging; treat with pelvic radiotherapy +/- vaginal brachytherapy
  - OR if patient has LVSI, consider enrolment in PORTEC-3/EN.7 Trial

Stage II

- Options include:
  - If radiologic imaging is negative, treat with pelvic radiotherapy and vaginal brachytherapy +/- para-aortic radiotherapy. For grade 3 tumours, chemotherapy may be added
  - If radiologic imaging is positive, treat with pelvic radiotherapy +/- vaginal brachytherapy +/- chemotherapy
  - OR consider enrolment in PORTEC-3/EN.7 Trial

Therapy for Relapsed Patients

The recurrence rate for endometrial cancer is approximately 20%. The majority (70%) of recurrences will be confined to the pelvis, while the remaining (30%) will be extrapelvic recurrences.

- Consider enrolment in a clinical trial.
- For pelvic recurrences, if no prior radiotherapy has been given to site of recurrence, then treat with EBRT plus brachytherapy or surgical exploration of the pelvis plus resection, with post-operative radiation therapy (PORT).
- For extrapelvic recurrences, treat with chemotherapy +/- hormone therapy +/- radiotherapy; if prior radiotherapy has been given to the site of recurrence, one of the following can be considered:
  - Surgical exploration of the pelvis plus resection, with or without PORT
  - Hormone therapy
  - Chemotherapy
- For isolated metastases, consider resection with or without radiotherapy. If the tumour is unresectable or if there is further recurrence, then treat as disseminated metastases (see below).
- For disseminated metastases, if asymptomatic or low grade, then treat with hormone therapy then chemotherapy. If symptomatic or grade 2/3, or large volume, the treat with chemotherapy and/or palliative radiotherapy.

Follow-up and Surveillance

The following suggestions for follow-up of women without evidence of disease after primary potentially curative treatment for any stage of endometrial cancer have been modified from the American College of Obstetricians and Gynecologists (2005) and Cancer Care Ontario (2006) follow-up guidelines (see the "Adaptation" field):

- Patient counseling on potential recurrence symptoms could include discussion of:
  - Unexplained vaginal bleeding or discharge
  - Detection of a mass
  - Abdominal distension
  - Persistent pain, especially in the abdomen or pelvic region

    - Fatigue
    - Diarrhea, nausea or vomiting
    - Persistent cough
    - Swelling
    - Weight loss
- Follow-up by the treating gynecologic oncologist, general gynecologist, or general practitioner could be based on the risk of recurrence. The majority of recurrences are symptomatic and occur within 5 years.
  A general examination, including complete history, speculum, and a pelvic-rectal examination, could be performed as follows:
    - Low-risk patients (i.e., stage IA or IB, grade 1 or 2): every 6 months during years 1 through 3, then once yearly during years 4 and 5.
    - High-risk patients (i.e., stage IA or IB, grade 3, or stage IC or advanced stage): every 3 to 6 months during years 1 through 3, then every 6 months during years 4 and 5.
- Patients who are symptomatic should undergo appropriate investigations to rule out recurrence, as many local recurrences are potentially curable with additional therapy.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Endometrial cancer

Note: There are several histological types of endometrial cancer. These include endometrioid and variants, such as ciliated cell adenocarcinoma, secretory adenocarcinoma, villoglandular, and adenocarcinoma with squamous differentiation, accounting for 75% to 80%; mixed, accounting for 10%; uterine papillary serous, accounting for <10%; clear cell, accounting for 4%; mucinous, accounting for 1%; squamous cell, accounting for <1%; and undifferentiated.

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Obstetrics and Gynecology

Oncology

Pathology

Radiation Oncology

Surgery

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To review endometrial cancer treatment options including surgery, radiotherapy, chemotherapy and hormone therapy

Target Population

Women with endometrial cancer, including uterine carcinosarcoma

Note: This guideline does not cover leiomyosarcoma and endometrial stromal sarcoma, which should be staged as uterine sarcomas. For recommendations on the management of uterine sarcomas, please refer to the National Guideline Clearinghouse (NGC) summary of the Alberta Health Services guideline Uterine sarcoma.

Interventions and Practices Considered

1. Surgery with pathology review
    - Hysterectomy with bilateral salpingo-oophorectomy (BSO), lymph node dissection, and omentectomy
    - Preoperative radiotherapy
    - Referral to gynecologic oncologist
2. Adjuvant treatment/management
    - Observation or no treatment
    - Pelvic radiotherapy
    - Vaginal vault brachytherapy
    - Whole pelvic radiation
    - Para-aortic radiotherapy
    - Enrolment in PORTEC-3/EN.7 trial
    - Hormone therapy (medroxyprogesterone, megestrol)
    - Chemotherapy (carboplatin, paclitaxel, docetaxel)
    - External beam radiotherapy (EBRT)
    - Palliative radiotherapy
    - Computed tomography (CT) scan of chest, abdomen, pelvis
    - Reoperation for surgical staging
3. Therapy for relapses
    - Enrolment in a clinical trial
    - EBRT plus brachytherapy
    - Surgical exploration of the pelvis plus resection with or without post-operative radiation therapy
    - Hormone therapy
    - Chemotherapy
    - Palliative radiotherapy
4. Follow-up and surveillance
    - Counseling patient about potential recurrence symptoms
    - Follow-up examinations based on risk of recurrence

Major Outcomes Considered

- Recurrence

- 5-year progression-free survival
- 5-year overall survival

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (Patient or Population, Intervention, Comparisons, Outcomes).

Guideline Questions

- Is chemotherapy following surgery in women diagnosed with endometrial cancer, at various stages and grade classifications more effective than surgery alone in preventing recurrence and/or improving progression free survival?
- Is radiation therapy following surgery in women diagnosed with endometrial cancer, at various stages and grade classifications more effective than surgery alone in preventing recurrence and/or improving progression free survival?
- Is hormone therapy following surgery in women diagnosed with endometrial cancer, at various stages and grade classifications more effective than surgery alone in preventing recurrence and/or improving progression free survival?

Search Strategy

Entries to the Medline, EMBASE, and Cochrane databases and clinical practice guideline databases were searched for evidence relevant to this topic. Search terms included: endometrial OR endometrium AND cancer OR carcinoma OR adenocarcinoma OR carcinosarcoma AND (1) chemotherapy OR carboplatin OR Taxol; or (2) brachytherapy OR radiotherapy OR radiation; or (3) progestogens OR megestrol OR Megace OR hormone; or (4) oophorectomy OR lymphadenectomy OR hysterectomy OR surgery.

Guidelines reviewed include the following: the National Comprehensive Cancer Network (NCCN) guidelines (2013), the European Society for Medical Oncology (ESMO) guidelines (2013), the BC Cancer Agency (BCCA) guidelines (2011), and Cancer Care Ontario (CCO) Program in Evidence-Based Care guidelines (2006–2007). All randomized controlled trials on the role of chemotherapy were reviewed from 1997 through to February 2011. The PORTEC-3/EN.7 trial was also reviewed.

The guideline was originally developed in 2009 and then updated in 2011, 2012, and again in 2013. The literature was reviewed prior to each update, using the search strategy described above.

Number of Source Documents

- A total of 46 studies were included through the 2011 review.
- The 2012 and 2013 reviews included a total of 13 studies and 11 studies, respectively.

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gynecologic Oncology Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Utilization Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (http://www.agreetrust.org) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Formulating Recommendations

The working group members formulated the guideline recommendations based on the evidence synthesized by the Knowledge Management (KM) Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field), the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the Guideline Utilization Resource Unit (GURU) does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

Following a review of the evidence by the Alberta Provincial Gynecologic Oncology Team, no major changes were made to the recommendations and the guideline was reaffirmed.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was reviewed and endorsed by the Alberta Provincial Gynecologic Oncology Tumour Team.

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management (KM) Specialist and the working group members, it is sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized. Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it will be officially endorsed by the Provincial Tumour Team Lead and the Executive Director of Provincial Tumour Programs.

Evidence Supporting the Recommendations

References Supporting the Recommendations

Gien L, Kwon J, Oliver T, Fung-Kee-Fung M, Gynecology Cancer Disease Site Group. Adjuvant hormonal therapy for stage 1 endometrial cancer: recommendations. Toronto (ON): Cancer Care Ontario (CCO); 2007 Oct 25. 19 p. (Evidence-based series; no. 4-14). [18 references]

Type of Evidence Supporting the Recommendations

The recommendations are partially adapted from existing guidance (see the "Adaptation" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Appropriate management and evidence-based care of women with endometrial cancer
- Prevention of recurrence and improved survival

Potential Harms

Chemotherapy-related toxicity

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gynecologic Oncology Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

End of Life Care

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Alberta Provincial Gynecologic Oncology Tumour Team. Endometrial cancer. Edmonton (Alberta): CancerControl Alberta; 2013 Sep. 15 p. (Clinical practice guideline; no. GYNE-002). [76 references]

Adaptation

The recommendations on follow-up and surveillance are modified from the following guidelines:

- American College of Obstetricians and Gynecologists (ACOG). ACOG Practice Bulletin, Clinical Management guidelines for obstetrician-gynecologists. Number 65, August 2005.
- Fung-Kee-Fung M, Dodge J, Elit L, et al., and the Gynecology Cancer Disease Site Group. Follow-up after Primary Therapy for Endometrial Cancer: A Clinical Practice Guideline. Program in Evidence-Based Care, Cancer Care Ontario. Evidence-based Series #4-9: Section 1; Report Date: January 10, 2006.

Date Released

2012 Apr (revised 2013 Sep)

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

CancerControl Alberta

There was no direct industry involvement in the development or dissemination of this guideline.

Guideline Committee

Alberta Provincial Gynecologic Oncology Tumour Team

Composition of Group That Authored the Guideline

Members of the Alberta Provincial Gynecologic Oncology Tumour Team include gynecologic oncologists, radiation oncologists, medical oncologists, pathologists, nurses, and pharmacists.

Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Gynecologic Oncology Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Gynecologic Oncology Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Gynecologic Oncology Tumour Team. Endometrial cancer. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2012 Apr. 16 p. (Clinical practice guideline; no. GYNE-002).

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Edmonton (Alberta): CancerControl Alberta; 2013 Jan. 5 p. Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 6, 2012. The information was verified by the guideline developer on January 14, 2013. This summary was updated by ECRI Institute on April 28, 2014. The updated information was verified by the guideline developer on May 22, 2014. This summary was updated by ECRI Institute on July 18, 2014 following the U.S. Food and Drug Administration advisory on Docetaxel.

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